Cardiopulmonary Support and Physiology

# Antegrade selective cerebral perfusion during operations on the thoracic aorta: Factors influencing survival and neurologic outcome in 413 patients

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**Objective:** We retrospectively analyzed hospital mortality and neurologic outcome after operations on the thoracic aorta with the aid of antegrade selective cerebral perfusion to determine a predictive risk model.

**Methods:** Between October 1995 and May 2001, 413 patients (mean age, 63.0 ± 11.5 years) underwent operations on the thoracic aorta with antegrade selective cerebral perfusion. Indications for surgical intervention were acute type A dissection in 116 (28.1%) patients, degenerative aneurysm in 227 (55.0%) patients, and postdissection aneurysm in 70 (16.9%) patients. One hundred twenty-five (30.3%) patients were operated on urgently; concomitant procedures were performed in 171 (41.4%) patients. Mean cerebral perfusion time was 63.0 ± 38.7 minutes (range, 16-220 minutes). Preoperative and intraoperative factors were evaluated by means of univariate and multivariate analysis to identify predictors of hospital mortality and neurologic outcome.

**Results:** The hospital mortality was 9.4%. Stepwise logistic regression revealed urgency status ($P$ = .000; odds ratio, 19.9) and recent history of a recent central neurologic event ($P$ = .004; odds ratio, 8.0) to be independent determinants for hospital mortality. Temporary neurologic dysfunction occurred in 20 (5.1%) patients. Urgency status ($P$ = .005; odds ratio, 7.5), history of a central neurologic event ($P$ = .003; odds ratio, 8.6), and coronary artery bypass grafting ($P$ = .019; odds ratio, 6.0) were independent determinants of temporary neurologic dysfunction. Urgency status ($P$ = .003; odds ratio, 8.6) was the only independent determinant for permanent neurologic dysfunction, and it occurred in 15 (3.7%) patients.

**Conclusion:** Antegrade selective cerebral perfusion is an effective method of brain protection. Cerebral perfusion times of longer than 90 minutes were not associated with an increased risk of hospital mortality or poorer neurologic outcome. Urgency status and recent history of central neurologic events were retained as important risk factors for hospital mortality and neurologic outcome.

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Despite gradual improvement of the results in operations on the aortic arch, brain injury remains the most feared complication and frequent cause of death.[1-7] Available techniques of cerebral protection include deep hypothermic circulatory arrest (DHCA) alone or in combination with retrograde cerebral perfusion (RCP) and antegrade selective cerebral perfusion (ASCP). All 3 methods have both advantages and disadvantages.

The purpose of our study was to evaluate the results of ASCP with moderate hypothermic circulatory arrest in patients undergoing operations of the proximal thoracic aorta, with particular emphasis on the predictors of hospital mortality and neurologic outcome.

## Patients and Methods

### Patients' Profiles

After defining common perioperative variables (see appendix), a total of 413 medical records of patients who underwent thoracic aortic operations with ASCP at the St Antonius Hospital (Nieuwegein, The Netherlands) and S. Orsola Hospital (Bologna, Italy) between October 1995 and May 2001 were retrospectively examined and included in the study.

There were 268 (64.9%) men and 145 (35.1%) women in the study, with an age range of 21 to 85 years (mean, 63.0 ± 11.5 years); 204 (49.4%) were older then 65 years. Of the entire cohort, 288 (69.7%) patients were operated on electively, and 125 (30.3%) underwent urgent operations (116 patients sustained acute dissection, and 9 sustained impending aneurysmal rupture). Indications for surgical intervention were acute type A dissection in 116 (28.1%) patients, chronic postdissection aneurysm in 70 (16.9%) patients, and degenerative aneurysm in 227 (55.0%) patients. Associated diseases included chronic obstructive pulmonary disease in 44 (10.7%) patients and chronic renal dysfunction (defined as a creatinine serum level $> 250$ $\mu$mol/L) in 14 (3.4%) patients. Twenty (4.8%) patients had a recent history of a central neurologic event (transient ischemic attack = 9, stroke = 11), and 60 (14.5%) had undergone previous aortic-cardiac surgical procedures through a median sternotomy. All patients having elective surgery underwent preoperative evaluation of cerebral circulation with Doppler ultrasonography of the extracranial vessels, digital subtraction angiography of the extracranial and intracranial circulation, carotid compression tests with monitoring by means of electroencephalography to evaluate occlusion intolerance, or a transcranial Doppler (TCD) ultrasonographic study.

### Operative Technique

Anesthetic management and methods of brain and myocardial protection were similar in both institutions. Induction of anesthesia was obtained with 2 mg/kg propofol, 2 $\mu$g/kg fentanyl, and 0.1 mg/kg pancuronium. Propofol and fentanyl were used for maintenance of anesthesia. For all patients, pH control was carried out by using the alpha-stat method.

A median sternotomy was used in 395 (95.6%) patients, and a median sternotomy plus anterolateral thoracotomy was used in 6 (1.4%) patients. In the remaining 12 (3%) patients, the diseased aorta was exposed through a left posterolateral thoracotomy. After systemic heparinization, cardiopulmonary bypass was instituted with a cannula for arterial return in the ascending aorta or in the femoral artery and a venous, single, 2-stage cannula in the right atrium or a long venous cannula through the left femoral vein into the right atrium. The left side of the heart was vented through the right superior pulmonary vein. Myocardial protection was achieved with cold crystalloid cardioplegia and topical pericardial cooling.

**TABLE 1. Overview of the extent of aortic replacement (n = 413)**

| Extent of replacement | No. | % |
|---|---|---|
| Ascending aorta + hemiarch | 214 | 51.8 |
| Ascending aorta + total arch | 138 | 33.4 |
| Total thoracic aorta | 18 | 4.4 |
| Arch + descending aorta | 13 | 3.1 |
| Isolated arch | 24 | 5.8 |
| Others | 6 | 1.5 |

Details of our cannulation technique and method of ASCP with moderate hypothermic circulatory arrest have been previously described.[8,9] In brief, after cardiopulmonary bypass was instituted and the patients were cooled to a nasopharyngeal temperature of 22°C to 26°C, systemic circulation was arrested, and the diseased aorta was opened. With the patient in the Trendelenburg position and under direct visual control, 15F retrograde coronary sinus perfusion cannulas (Medtronic DLP; Chase Medical Inc, Houston, Tex) connected to the oxigenator with a separate single-roller pump head were inserted into the innominate and left common carotid arteries through the aortic lumen. After the cannulas were properly placed, the balloons at the tip of the cannulas were manually inflated and held in place with an encircling tape. The left subclavian artery was clamped or occluded with a Fogarty catheter (Baxter Healthcare Corporation, Irvine, Calif; IFM, Clearwater, Fla) to avoid the steal phenomenon.

Cerebral perfusion was started at a rate of 10 $mL \cdot min^{-1} \cdot kg^{-1}$ and adjusted to maintain a right radial arterial pressure between 40 and 70 mm Hg. The introduction of the cerebral perfusion catheters usually took less than 3 minutes.

During open distal anastomosis,[10,11] blood perfusion to the lower half of the body from the femoral artery, when cannulated, was arrested or reduced to 500 mL/min.

Tools of cerebral monitoring included a right radial arterial pressure line in all cases, electroencephalogram, regional oxygen saturation in the bilateral frontal lobes by means of near-infrared spectroscopy (NIRS), and TCD measurement of the blood velocity of the middle cerebral artery to confirm the proper placement and function of both cannulas when available. Transesophageal echocardiography was routinely used to assess cardiac contractility, blood flow conditions, aortic disease, and intracardiac air.

The extent of the aortic replacement and the associated procedures are listed in Tables 1 and 2.

En bloc[12] or separated graft techniques were used to reimplant the arch vessels when a complete aortic arch replacement was performed.

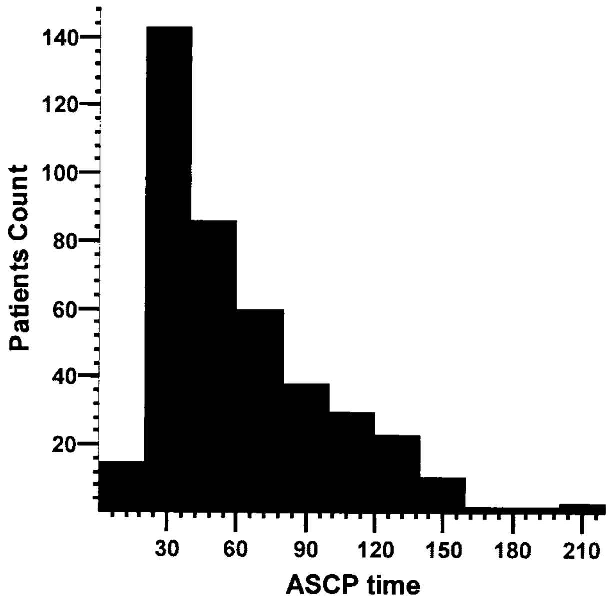


**Figure 1. Distribution of patients on the basis of antegrade selective cerebral perfusion *(ASCP)* time.**

### Definitions of Neurologic Complications

Patients were considered to have had permanent neurologic injuries if they exhibited the presence of new neurologic dysfunction after surgical intervention, whether focal injury (stroke) or global (coma) dysfunction, or were found to have new focal or multiple brain lesions confirmed by means of brain computed tomographic (CT) scanning or magnetic resonance imaging.

Transient neurologic dysfunction (TND), as defined by Ergin and associates,[13] indicated the occurrence of postoperative confusion, agitation, delirium, prolonged obtundation, or transient parkinsonism with negative brain CT scans and complete resolution before discharge.

### Statistical Analysis

Continuous variables were expressed as means ± 1 SD, and categorical variables were expressed as percentages. All preoperative and intraoperative variables were first analyzed by univariate analysis (unpaired 2-tailed *t* tests, $\chi^2$ tests, or Fisher exact tests when appropriate) to determine whether any single factor influenced hospital mortality and neurologic outcome. The analysis for permanent neurologic dysfunction and TND were conducted separately. Risk factors for permanent neurologic dysfunction were examined in all patients who survived the operation long enough to undergo neurologic evaluation, and risk factors for TND were assessed in all operative survivors without permanent neurologic dysfunction. Variables that achieved a *P* value of less than .05 in the univariate analysis were examined with multivariate analysis by using forward stepwise logistic regression to evaluate independent risk factors for hospital mortality, permanent neurologic dysfunction, and TND.

Statistical analysis was performed with SPSS 7.0 statistical software (SPSS, Inc, Chicago, Ill).

**TABLE 2. Overview of the concomitant procedures**

| Procedures | No. | % |
|---|---|---|
| Aortic valve replacement | 44 | 10.7 |
| Bentall procedure | 103 | 24.9 |
| Aortic valve–sparing procedure | 15 | 3.6 |
| Aortic valve suspension | 9 | 2.2 |
| Homograft | 2 | 0.5 |
| Elephant trunk | 78 | 18.9 |
| CABG | 13 | 3.1 |

*CABG,* Coronary artery bypass grafting.

## Results

### Cardiopulmonary Bypass Data

The mean cardiopulmonary bypass time was 201 ± 62 minutes (range, 85-493 minutes), and the mean myocardial ischemic time was 124 ± 45 minutes (range, 28-280 minutes). The mean ASCP time was 63 ± 39 minutes (range, 16-220 minutes; Figure 1). A total of 235 (56.9%) patients had an ASCP time of greater than 45 minutes, and 90 (21.8%) had an ASCP time of greater than 90 minutes.

### Hospital Mortality

Operative mortality was 0.9% (4/413). Thirty-nine patients died during hospitalization, for an overall in-hospital mortality of 9.4%. The hospital mortality was 13 (4.5%) of 288 patients undergoing elective and 26 (20.8%) of 125 patients undergoing urgent surgical intervention (*P* = .000). Causes of death were multiorgan failure (n = 15), septic shock (n = 4), neurologic damage (n = 2), myocardial infarction (n = 2), low cardiac output (n = 4), bleeding (n = 4), bowel ischemia (n = 2), rupture of a distal aneurysm (n = 5), and rupture at a proximal anastomotic site (n = 1).

On univariate analysis, the following factors had a significant influence on hospital mortality: urgent status (*P* = .000), acute dissection (*P* = .000), history of a recent central neurologic event (*P* = .001), and preoperative renal insufficiency (*P* = .034). Multivariate analysis revealed urgent status (*P* = .000; odds ratio [OR], 19.9) and history of a recent central neurologic event (*P* = .004; OR, 8.0) to be independent predictors of hospital mortality (Table 3). The extent of aortic replacement and ASCP duration of greater than 90 minutes were not statistically correlated with an increased risk of hospital mortality.

In 287 patients who underwent elective operations, univariate analysis indicated age greater than 65 years (*P* = .003), chronic obstructive pulmonary disease (*P* = .014), preoperative renal insufficiency (*P* = .046), and history of a recent central neurologic event (*P* = .057) as adverse risk factors for hospital mortality. In the same group of patients, significant predictors of hospital mortality after multivariate analysis were age greater than 65 years (*P* = .012; OR, 6.1) and history of a recent central neurologic event (*P* = .017; OR, 5.6).

**TABLE 3. Univariate and multivariate analysis for hospital mortality (n = 413)**

| Variable | No. of patients | No. of hospital deaths (%) | Univariate analysis (*P* value) | Multivariate analysis (*P* value) | OR |
|---|---|---|---|---|---|
| Acute dissection | | | .000 | | |
| Yes | 116 | 24 (20.6) | | | |
| No | 297 | 15 (5) | | | |
| Urgency | | | .000 | .000 | 19.9 |
| Yes | 125 | 26 (20.8) | | | |
| No | 288 | 13 (4.5) | | | |
| History of neurologic event | | | .001 | .004 | 8.0 |
| Yes | 20 | 7 (35) | | | |
| No | 393 | 32 (8.1) | | | |
| Preoperative renal insufficiency | | | .034 | | |
| Yes | 14 | 4 (28.5) | | | |
| No | 399 | 35 (8.7) | | | |

### Hospital Morbidity

Permanent neurologic dysfunction, which was evaluated in all patients who survived the operation long enough to undergo an adequate neurologic examination, was reported in 15 (3.7%) of 405 patients. Four (0.9%) patients never regained consciousness after the operation; a brain CT scan showed multiple cerebral infarctions in these patients, and in 11 (2.7%) patients a focal injury was diagnosed.

In univariate analysis acute dissection ($P$ = .007) and urgent status ($P$ = .003) showed statistically significant correlation with the occurrence of permanent neurologic dysfunction. On multiple logistic regression analysis, urgent status ($P$ = .003; OR, 8.6) was found to be an independent predictor of permanent neurologic dysfunction (Table 4).

TND, which was evaluated only in patients without permanent neurologic damages, occurred in 20 (5.1%) of 390 patients.

Acute dissection ($P$ = .006), urgent status ($P$ = .003), history of a recent central neurologic event ($P$ = .002), and coronary artery bypass grafting (CABG; $P$ = .019) were associated with a significantly increased risk of TND on univariate analysis. Stepwise logistic regression indicated urgent status ($P$ = .005; OR, 7.5), history of a recent central neurologic event ($P$ = .003; OR, 8.6), and CABG ($P$ = .013; OR, 6.0) as independent predictors of TND (Table 5). ASCP duration of greater than 90 minutes was not a significant risk factor for permanent neurologic dysfunction or TND.

In the group of patients undergoing elective operations, univariate assessment revealed CABG ($P$ = .023) and aortic valve replacement ($P$ = .049) to be associated with TND.

Other postoperative complications were bleeding requiring a repeat thoracotomy in 61 (14.8%) patients and postoperative myocardial infarction (serum creatine phokinase level > 300 IU/L with a creatine kinase MB fraction > 3%) in 14 (3.4%) patients. Pulmonary complications requiring mechanical ventilatory support for longer than 5 days occurred in 57 (13.8%) patients; 25 of them underwent urgent operations ($P$ < .001). Renal failure requiring temporary haemodialysis occurred in 20 (4.8%) patients, and 11 of them underwent urgent operations ($P$ < .001).

## Discussion

Although results of aortic arch surgery have improved in recent decades, neurologic injuries resulting from interruption of cerebral circulation remain the most feared complications and frequent cause of death. Available methods of cerebral protection include DHCA with or without RCP and ASCP.

DHCA provides a still, bloodless operative field and is technically less complicated. The aortic arch and arch vessels can be carefully inspected, and manipulation can be avoided, resulting in reduced cerebral embolic risk. However, this technique has the disadvantage of a limited safe time of circulatory arrest,[1,14,15] and a prolonged cardiopulmonary bypass time is required to cool down and rewarm the patient, which might result in a number of pulmonary, renal, and cardiac endothelial dysfunctions, as well as increased microembolism production.[1,2,16] Coagulative complications are associated with deeper levels of hypothermia. We believe DHCA to be an excellent method of brain protection when a circulatory arrest time of less than 30 minutes is anticipated.

RCP was introduced in aortic arch surgery to prolong the safe time of circulatory arrest.[17] Flushing of embolic material,[18] cerebral metabolic support,[19,20] catabolite removal, and enhanced cerebral hypothermia maintenance[21] are the supposed neuroprotective mechanisms, but these still remain controversial. Moreover, Griepp and colleagues[22] experimentally found that RCP, especially at high pressure, although successful in removing some emboli, might result in cerebral injuries.[18] We had a very limited experience with RCP, with results similar to those obtained with DHCA alone.

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**TABLE 4. Univariate and multivariate analysis for permanent neurologic dysfunction (n = 405)**

| Variable | No. of patients | No. of PNDs (%) | Univariate analysis (*P* value) | Multivariate analysis (*P* value) | OR |
|---|---|---|---|---|---|
| Acute dissection | | | .007 | | |
| Yes | 110 | 9 (8.2) | | | |
| No | 295 | 6 (2.0) | | | |
| Urgency | | | .003 | .003 | 8.6 |
| Yes | 119 | 10 (8.4) | | | |
| No | 286 | 5 (1.7) | | | |

*PND,* Permanent neurologic dysfunction.

**TABLE 5. Univariate and multivariate analysis for temporary neurologic dysfunction (n = 390)**

| Variable | No. of patients | No. of TNDs (%) | Univariate analysis (*P* value) | Multivariate analysis (*P* value) | OR |
|---|---|---|---|---|---|
| Acute dissection | | | .006 | | |
| Yes | 101 | 11 (10.9) | | | |
| No | 289 | 9 (3.1) | | | |
| Urgency | | | .003 | .005 | 7.5 |
| Yes | 109 | 12 (11) | | | |
| No | 281 | 8 (2.8) | | | |
| History of neurologic event | | | .002 | .003 | 8.6 |
| Yes | 19 | 5 (26.3) | | | |
| No | 371 | 15 (4) | | | |
| Concomitant CABG | | | .019 | | 6.0 |
| Yes | 12 | 3 (25) | | | |
| No | 378 | 17 (4.5) | | | |

*TND,* Temporary neurologic dysfunction; *CABG,* coronary artery bypass grafting.

ASCP, as described by Kazui and colleagues[11] is our first-choice method of cerebral protection. It prolongs the safe time of circulatory arrest,[8,9,23] improves cerebral cooling, and can be used with moderate hypothermia. Suggested drawbacks of this technique include greater complexity, a cumbersome operative field, and manipulation and cannulation of the arch vessels, especially in the presence of cloth, loose atheroma, or dissection. In our series the mean ASCP time was 63 minutes, whereas 51.8% of patients had only hemiarch replacement. Indeed, when ASCP is used, the procedure takes a slightly longer time. However, this mean ASCP time was largely influenced by more complex and time-consuming operations, such as aortic arch replacement with the separated graft technique, in which ASCP continued until the concluding anastomosis for the left common carotid artery was performed. Actually, in the subgroup of patients undergoing hemiarch replacement, the mean ASCP time was 40 ± 20 minutes (elective repair, 35 ± 19 minutes; urgent repair, 47 ± 17 minutes; $P$ = .001). In our experience the time required to prepare the aortic arch and to introduce the cannulas into the arch vessels was always less then 3 minutes. Our ASCP cannulas are flexible, made of silicon, and can be placed toward the patient's head, so as not to obscure the operative field. The potential risk of brain embolism can be reduced by means of the separated graft technique, in which the origin of the arch vessels is resected and replaced with an aortic arch branched graft. In cases of acute dissection, it has always been easy to distinguish the true lumen for arch vessel cannulation. Malpositioning of the ASCP cannulas is easily and immediately recognized by means of TCD and NIRS measurements.

In this multicenter study postoperative neurologic complications were classified into 2 groups: temporary and permanent neurologic dysfunction. The temporary neurologic dysfunction seems to be a manifestation of subtle but diffuse brain injury associated with long-lasting cognitive impairment[24] that is undetectable by means of conventional imaging techniques and directly correlated to inadequate brain protection.

Ergin and associates[13,24] reported an overall TND rate of 19% to 28% using DHCA, and an almost linear relationship between circulatory arrest time and the occurrence of TND was found. Reich and coworkers[15] demonstrated that a DHCA time of 25 minutes or greater and advanced age are associated with memory and fine motor skills deficits and with prolonged hospital stay. Okita and colleagues[25] reported an incidence of severe TND of 25% in 148 patients who underwent operations on the aortic arch with DHCA and RCP. The same authors,[26] in a recent prospective study comparing DHCA with RCP and ASCP, reported a significantly higher incidence of TND in the RCP group (33% vs 13.3%, $P = .05$), especially when the RCP duration was greater than 50 minutes. A significant correlation between the degree of TND and the duration of brain circulatory arrest was also demonstrated. Hagl and colleagues[27] reported a higher rate of TND with RCP than with ASCP in a group of 91 patients who required a cerebral protection time of between 40 and 80 minutes. Furthermore, RCP resulted in no reduction of TND compared with DHCA alone.

In our experience the overall incidence of TND was 5.1%. Although we did not perform extensive psychologic testing, as in the studies by the abovementioned groups, which might underestimate our true incidence of TND, the difference is striking. An ASCP time of greater than 90 minutes was not significantly correlated with an increased risk of TND. Because our ASCP is performed with moderate hypothermic circulatory arrest (nasopharyngeal temperature, 22°C-26°C) instead of profound hypothermia, a shorter rewarming period is required. This probably results in a reduced risk of microembolism and in a better neurologic outcome. Stepwise logistic regression indicated urgent status, history of a recent central neurologic event, and CABG as independent predictors of TND. CABG as an independent risk factor for TND confirms our findings in a previous study[8]; it might be speculated[28] that the presence of coronary artery disease, and therefore the necessity of CABG, might be a further indication of cerebrovascular disease in these patients, which puts them at higher risk of cerebral dysfunction postoperatively.

In this series the overall hospital mortality was 9.4%, and the permanent neurologic dysfunction rate was 3.6%. This compares favorably with other reports. Kazui and colleagues[23] reported an early mortality of 12.7% in a group of 220 consecutive patients undergoing total arch replacement with the aid of ASCP. In that series the incidence of permanent neurologic dysfunction was 3.3%. Preoperative renal failure, pump time of greater than 300 minutes, early series, and shock were independent determinants of hospital mortality, whereas old cerebral infarction and pump time of greater than 300 minutes were independent determinants for permanent neurologic dysfunction. No statistical correlation between ASCP time and hospital mortality or adverse neurologic outcome was found. In 656 patients undergoing aortic surgery with DHCA, Svensson and colleagues[1] reported a hospital survival and stroke rate of 88% and 7%, respectively. An increased risk of stroke in patients treated with periods of circulatory arrest of greater of 40 minutes and an increased early mortality for circulatory arrest time of greater than 65 minutes were observed. Ueda and associates[29] reported a hospital mortality of 10% and a stroke rate of 4% in 249 patients undergoing aortic arch surgery with RCP as a method of brain protection. RCP time, pump time, and advanced age were indicated as risk factors for hospital mortality on multivariate analysis.

In the 413 patients analyzed in this study, urgent status and history of a recent central neurologic event were indicated as independent determinants of hospital mortality on multivariate analysis. When the elective cases where considered separately, age greater than 65 years emerged as a further adverse risk factor for hospital mortality. Urgent status was again statistically correlated with an increased risk of permanent neurologic dysfunction and TND together with a history of cerebrovascular disease and CABG. Patients undergoing urgent operations had an increased risk of pulmonary and renal postoperative complications. Looking at these findings, which are consistent with those of other reports,[1,23,27,28] we speculate that a more aggressive operative timing with an earlier elective aortic repair is probably necessary in patients at risk of rupture. Furthermore, the contribution of advanced age to hospital mortality might also be reduced. However, in patients with a history of cerebrovascular disease, further improvements in cerebral protection techniques are required.

In conclusion, ASCP is an effective and safe method of brain protection, allowing time-consuming aortic repairs to be performed, with encouraging results in terms of hospital mortality and neurologic outcome. Urgency status and recent history of a central neurologic event still remain important preoperative risk factors for hospital mortality and neurologic outcome.

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## Appendix.

### Preoperative, intraoperative, and postoperative variables included in the analysis

Age >65 years
Sex
Acute dissection
Status (elective-urgent)
Preoperative renal insufficiency (creatine >250 μmol/L)
Chronic obstructive pulmonary disease
History of recent central neurologic event (6 months)
Previous cardiovascular surgery through median sternotomy
Extent of replacement (hemiarch, arch, ascending aorta plus arch, total thoracic aorta, arch plus descending aorta, other)
Concomitant aortic valve replacement
Concomitant aortic valve–sparing procedures
Concomitant aortic valve suspension
Concomitant Bentall procedure
Concomitant homograft
Concomitant CABG
Elephant trunk
Cardiopulmonary bypass time of greater than 180 minutes
Myocardial ischemic time of greater than 120 minutes
Selective cerebral perfusion time of greater than 90 minutes
Exitus
Postoperative respiratory failure
Postoperative myocardial infarction
Postoperative hemodialysis
Bleeding requiring rethoracotomy
Permanent neurologic dysfunction
Temporary neurologic dysfunction